as filed, especially on pages 32-33 and in Example 10 on pages 43-44. No new matter has been added.

IDS

Applicants thank the Examiner for initialing and returning Form PTO 1449. Applicants note, however, note that reference AD (Elbashir *et al.*, Nature 2001 15:188-200) was not initialed. Applicants enclose for the Office's convenience another copy of the Elbashir reference as well as a copy of the otherwise completed Form PTO 1449. Applicants respectfully request consideration of the Elbashir reference.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-3 and 19 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description. Applicants respectfully disagree because the specification sufficiently describes the claimed subject matter.

"The purpose of the adequate written description requirement is to ensure that the inventor had possession of the claimed subject matter at the time the application was filed. If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." *In re Alton,* 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996).The first paragraph of section 112 requires Applicants to describe the subject matter ***defined by the claims***. *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985)(emphasis added); *In re Wilder*, 736 F.2d 1516, 1520 (Fed. Cir. 1984). An originally filed claim is part of the specification and is thus disclosure that can be relied upon as disclosure, M.P.E.P. §608.01(l); *In re Gardner*, 178 U.S.P.Q. 149 (C.C.P.A. 1971), and as "written description." The PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. *In re Wertheim,* 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976).

The Examiner states that "the specification discloses SEQ ID NO:2 which corresponds to a human RNAse III" and acknowledges that "SEQ ID NO:2 meets the

written description provisions of 35 USC §112, first paragraph." (Office Action at page 3). However, the Examiner alleges that as "the claims are directed to encompass mutated sequences, allelic variants, splice variants, sequences that have a recited degree of homology . . . [n]one of these sequences meet the written description provision of 35 USC 112, first paragraph." (Office Action at page 3). The Examiner cites *Vas-Cath, Inc. v. Mahurkar* and *University of California v. Eli Lilly and Co.* as support for the allegation that the pending claims fails to comply with the written description requirement.

As amended, pending claim 1 recites an isolated human RNase III polypeptide comprising human RNase III which cleaves double-stranded RNA. Claim 2 recites an RNase III polypeptide comprises an amino acid sequence which is at least 90% homologous to SEQ ID NO:2. Claim 3 recites that the isolated human RNase III polypeptide of claims 1 or 2 comprises the amino acid sequence of SEQ ID NO:2. Claim 19 depends from claim 4 and recites a composition comprising the isolated human RNase polypeptide further comprising an antisense oligonucleotide.

Preliminarily, Applicants note that claim 4 was not rejected under 35 U.S.C. § 112, first paragraph. However, Applicants respectfully point that claim 19, depending from claim 4, was rejected under 35 U.S.C. § 112, first paragraph and note that the Examiner failed to specifically address the rejection of claim 19 under 35 U.S.C. § 112, first paragraph.

Written description support for the claims is present throughout the application as filed. For example, as discussed above, claims 1-3 are substantially as originally filed and therefore serve as "written description." Additional written description support for claims 1-3 and 19 can be found throughout the application as originally filed. The application as filed provides nucleotide and amino acid sequences for human RNase III (see SEQ ID NOS:1 and 2, respectively). The present application sets forth methods for identifying RNase III polypeptides which cleave double-stranded RNA (*see*, for example, Example 10). The present application also provides several examples of species of human RNase III polypeptides. For example, synthetic RNase III peptides were generated and used to prepare domain-specific antibodies (page 8, lines 11-18, and Example 6, citing SEQ ID NOS:35 and 36), and a fragment of the human RNase III polypeptide was expressed as a GST-RNase III fusion protein and used to demonstrate

that the RNase III domain-coding region alone can act as a dsRNase (page 32, lines 27-30 and Example 9). The application further provides the results of homology analyses between human, *C. elegans* (Worm; SEQ ID NO:3), *S. pombe* (PAC; SEQ ID NO:4), *S. cervisiae* (RNT; SEQ ID NO:5), and *E. coli* (RNC; SEQ ID NO: 6) RNase III (see Figure 1) and recites the amino acid identity of human RNase III to Worm (41%), PAC (17%), RNT (15%) and RNC (16%)." (see page 4, line 32 to page 5, line 7). As set forth on pages 35 and 39 of the application as filed, these homology analyses were performed via the internet on the NCBI database (*e.g.* using XREFdb/BLAST). Thus, the inventors were clearly in possession of several species within the claimed genus at the time of filing.

The PTO has promulgated guidelines for the application of the written description requirement in "Revised Interim Written Description Guidelines Training Materials". Applicants respectfully direct the Examiner's attention to the Examples set forth therein, one of which is reproduced below:

> **Example 14: Product by Function**
> **Specification:** The specification exemplifies a protein isolated from liver that catalyzes the reaction of A→ B. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.
> **Claim:**
> A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A→ B.
> **Analysis:**
> A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.
> A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity

to the SEQ ID NO: 3. Additionally, the claim is drawn to a protein which **comprises** SEQ ID NO:3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising".

The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.

A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.

There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

Conclusion: The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.

Applicants respectfully assert that the claimed invention complies with the written description requirement of 35 U.S.C. §112, first paragraph. Claim 2 is analogous to the exemplary claim recited in Example 14 of the Examination Guidelines set forth above, minus the requirement in the exemplary claim of a catalytic activity. In the exemplary claim, variants having 95% sequence identity (homology) to SEQ ID NO: 3 are recited. The analysis set forth in the Guidelines states that "the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must . . . have at least 95% identity to the reference sequence, SEQ ID NO: 3. . ." and that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 . . .". The Guidelines further state that "[o]ne of skill in the art would

conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus" and that "the disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention."

Applicants respectfully assert that the genera of proteins claimed comply with the written description requirement. For example, Applicants provide representative species of the genus (*see* SEQ ID NOS:35 and 36, for example). The genus encompassed by claim 1 does not have substantial variation since all species within the genus must cleave double-stranded RNA. The genus encompassed by claim 2 does not have substantial variation since all of the species within the genus must have at least 90% identity to SEQ ID NO: 2. Applicants provide a stated degree of homology (90%) which imposes a structural relationship between members of the genus. Applicants also provide methods for determining whether a polypeptide cleaves double stranded RNA (Example 10) and for determining homology and exemplary results (see page 4, line 32 to page 5, line 7; and page 39).

Applicants are ***not*** required to provide a specification that describes anything and everything upon which the claims could ever be construed to read. If Applicants were held to such a standard, no specification could ever be deemed to meet the written description requirement. As previously discussed, the specification adequately describes ***the subject matter defined by the present claims***, which is all that the law requires.

The Office Action has failed to provide any evidence or reasoning why the specific species described, along with a description of the attributes and features of the human RNase III that comprise the claimed genera, does not constitute adequate description of the claimed subject matter. One of skill in the art would conclude that Applicants were in possession of the necessary common attributes possessed by the members of the genus and that the disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.

Vas-Cath and *University of California* were cited to support the Office's assertion that the pending claims do not satisfy the Written Description requirement. Applicants respectfully assert that persons of ordinary skill in the art would recognize that Applicants invented what is claimed. As discussed above, the pending claims provide written description support for themselves as they are identical or substantially identical

to those originally filed. Applicants remind the Examiner that additional written description support is found throughout the application as originally filed and, thus, the citation of *Vas-Cath* does nothing to support the Examiner's position.

The citation of *University of California v. Eli Lilly and Co.* is distinguishable from the present facts. The Revised Interim Written Description Guidelines Training Materials discusses the *University of California* scenario in Example 7 and state that the exemplary claim (An isolated DNA comprising SEQ ID NO: 16) does not satisfy the written description requirement because "[t]he present claim encompasses full-length genes and cDNAs that are not further described. There is substantial variability among the species of DNAs encompassed within the scope of the claims of *University of California* because SEQ ID NO:16 is only a fragment of any full-length gene or cDNA species. When reviewing a claim that encompasses a widely varying genus, the examiner must evaluate any necessary common attributes or features."

Again, as discussed in greater detail above, the pending claims satisfy the written description guidelines because, *inter alia*, there is no "substantial variation among the species of DNA" – there are several "necessary common attributes or features". In the context of claim 1, Applicants respectfully point out that a common feature of each species is that it must cleave double stranded RNA. In the context of claim 2, a minimum of 90% sequence homology is required to SEQ ID NO:2. Further, several representative species are specifically set forth throughout the application. Applicants respectfully point out that the facts relating to the pending claims are analogous to Example 14 of the "The Revised Interim Written Description Guidelines Training Materials", in which the exemplary claim satisfies the Written Description Requirement.

The Office cites Wu, *et al* (J. of Biological Chemistry Vol. 275, No. 47:36957-36965, 2000, hereinafter referred to as the "Wu reference") as allegedly presenting evidence that "the species specifically disclosed are not representative of the genus because the genus is highly variant." Applicants respectfully disagree.

The Wu reference cites variability of known RNase III proteins across animal species, while the present invention discloses variability of the human RNase III polypeptide within the human species. The **inter**species variability cited on page 36957,

column 2, last paragraph of Wu (which states that "the human enzyme is distinctly different from the homologues in other species") describes RNase III **inter**specific homologues in other eukaryotes. **Inter**specific variablitiy is not equivalent to **intra**species variability observed within the genus of human RNase III polypeptides, much less to the limited variability present in polypeptides capable of cleaving double-stranded RNA or amino acid sequences having 90% sequence homology to SEQ ID NO:2, as claimed in claims 1 and 2, respectively. While **inter**species homology of the human RNase III protein of the invention is discussed in several parts of the present application (including page 6, lines 30-35, and page 7, lines 3-7, which describe a comparison of a human, RNase III amino acid sequence with RNase III amino acid sequences of other species) these other non-human species are not claimed -- Applicants claim ***human*** RNase III polypeptides. RNase III polypeptides which do not cleave dsRNA fall outside the scope of claim 1. The maximum variation of species within claim 2, for example, is 90%. In stark contrast, in terms of **inter**species sequence homology, the closest RNase III to the human RNase III is in worm and shares only 41% sequence homology. Wu fails to support the Examiner's assertion that "the species specifically disclosed are not representative of the genus because the genus is highly variant."

For the foregoing reasons, Applicants respectfully request withdrawal of the written description rejection. Accordingly, reconsideration and withdrawal of this rejection is requested.

Rejection Under 35 U.S.C. §102(a)

Claims 1-4 and 19 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Wu *et al.* (J. Biol. Chem., Vol. 275(47):39657-36965). Applicants respectfully traverse.

The publication date of the Wu reference is November 2000 which is within one year of the filing date, July 6, 2001, of the present application. Thus, Applicants submit herewith a Declaration of Dr. Hongjiang Wu under 37 CFR 1.131, in which Dr. Wu avers that he is a co-author of the Wu reference. Thus, Dr. Wu was clearly in possession of the claimed inventions prior to the publication of the Wu reference. Further, in the

declaration, Dr. Wu states that the additional co-authors of the Wu reference (Hong Xu and Loren J. Miraglia) were working under his direction or the direction of other representatives of the assignee of the present application...(Declaration at ¶3). Thus, the Wu reference should no longer be considered prior art. Accordingly, Applicants respectfully request the reconsideration and withdrawal of the rejection under 35 U.S.C. §102(a).

Applicants note that the 35 U.S.C. § 102 rejection was the only rejection pending against claim 4 and respectfully request an early indication that claim 4 is allowed.

Change of Correspondence Address

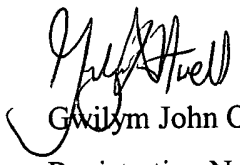
As set forth on the attached "Change of Correspondence Address" form SB-122, Applicants respectfully requests that all future correspondence related to this application be directed to:

Gwilym J. O. Attwell
COZEN O'CONNOR, P.C.
1900 Market Street
Philadelphia, PA 19103-3508
Telephone: (215) 665-2000
Facsimile: (215) 701-2004

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

The examination of these claims and passage to allowance are respectfully requested. An early Notice of Allowance is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 665-5548 to clarify any unresolved issues raised by this response.

Respectfully submitted,



Gwilym John Owen Attwell
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Date: April 16, 2003
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Version with markings to show changes made

In the Specification

Please amend the specification as follows:

Please amend the paragraph bridging pages 2 and 3 as follows:

RNA interference (RNAi) is a form of sequence-specific, post-transcriptional gene silencing in animals and plants, elicited by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene. Elbashir et al., *Nature*, **2001**, 411, 494-498. dsRNA triggers the specific degradation of homologous RNAs, only within the region of homology. The dsRNA is processed to 21- to 23-nucleotide fragments, sometimes called short interfering RNAs (siRNAs) which are believed to be the guide fragments for sequence-specific mRNA degradation. The processing of longer dsRNA to these short siRNA fragments is believed to be accomplished by [RNA] RNase III. Elbashir et al., ibid., Elbashir, et al., *Genes and Devel.*, **2001**, 15, 188-200. Thus it is believed that the human RNase III of the present invention may be useful in further understanding and exploiting the RNAi mechanism, particularly in human cells.

Please amend the paragraph bridging pages 27 and 28 as follows:

Antisense inhibition of human RNase III expression was used to further evaluate the role(s) of RNase III. To identify optimal sites in RNase III mRNA for antisense effects, 2'-O-methoxyethyl chimeric antisense oligonucleotides targeted to 10 sites in the mRNA were designed and screened for inhibition of RNase III. These are shown in Table 1. These chimeric or "gapped" oligonucleotides are designed to serve as substrates for RNase H when bound to RNA resulting in degradation of the target RNA and oligonucleotides of this type have been shown to be highly specific when used under the [dexcribed] described conditions.

In the Claims:

Please amend claims 1-3 as follows:

1. **(Amended)** An isolated human RNase III polypeptide [comprising human RNase III] which cleaves double-stranded RNA.

2. **(Amended)** An [The] isolated human RNase polypeptide III [of claim 1] which comprises an amino acid sequence which is at least 90% homologous to SEQ ID NO: 2.

3. **(Amended)** The isolated human RNase polypeptide of claim 1 or 2 which comprises the amino acid sequence of SEQ ID NO: 2.